IAF-14

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	John M. Ford
Group Art Unit	:	1202
Applicants	:	Coates et al.
Serial No:	:	07/835,964
Filed	:	February 20, 1992
For	:	1,3-OXATHIOLANE NUCLEOSIDE ANALOGUES

DECLARATION OF RICHARD STORER
UNDER 37 C.F.R. § 1.132

I, Richard Storer, declare and state as follows:

1. I am a co-inventor of the subject matter described and claimed in United States patent application 07/835,964, filed February 20, 1992 ("the '964 application"). I have read the September 15, 1993 Office Action issued in that application. I have also read United States patents 5,047,407 (Belleau) and 5,204,466 (Liotta) and PCT application WO 91/11186 (Liotta), cited by Examiner Ford in that Office Action. I am knowledgeable and experienced in the chemical and the medical technologies described in these patents and patent applications.

2. I obtained the degree of Bachelor of Science with honors in chemistry in 1968 and the degree of Doctor of Philosophy in chemistry in 1972, both from the University of

Sussex, England. I subsequently undertook post-doctoral research at the University of Cardiff and the University of Nottingham in the United Kingdom.

I have been employed by Glaxo at Greenford, England, since 1973 and since 1988 I have held the post of Research Manager in the Medicinal Chemistry Department. From 1984 until 1993 I was actively involved in the antiviral area. I have held various positions of scientific responsibility for Glaxo's work in this field and also have had line management responsibility for the chemistry resource. I am an author or co-author of fifty patents and publications in the antiviral area, many of which describe work in the nucleoside field. I have presented lectures on my work in this area at both national and international meetings including the 9th Nucleosides and Nucleosides Round Table in Uppsala, Sweden, 1990; the American Chemical Society meeting in Washington, D.C. August 1992 and the First International Symposium on Anti-infective Agents in Cambridge, England, in 1992. In the latter case I was a member of the organizing committee. I have also been asked to referee prospective publications dealing with the subject of antiviral nucleosides.

3. I make this declaration to set forth what was known about the chemistry and biology of antiviral nucleosides at the filing date of the '964 application and why the antiviral activity of (-)-cis-4-amino-1-(2-

hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one ("the (-)-enantiomer") was a significant and surprising discovery and advance in the field of antiviral therapeutics.

I also make this declaration to address Examiner Ford's comments about the 5% (+)-enantiomer, 95% (-)-enantiomer mixture of claim 3 of the '964 application.

4. The (-)-enantiomer belongs to a class of antiviral compounds known as "nucleoside analogues". At the filing date of the '964 application, I and those skilled in the art generally believed, that antiviral nucleoside analogues inhibited viral growth and replication by mimicking natural nucleosides; i.e. they had a molecular mimicry mechanism of action. We believed the mechanism of such inhibition to be that during viral growth and replication the viruses mistook the nucleoside analogues for natural nucleosides and attempted to incorporate them. If this attempt was unsuccessful, the virus growth was terminated, or at least hindered. On the other hand, if the nucleoside analogue was incorporated, its presence in the chain would prevent or disrupt viral growth. The analogues, thus, suppressed or inhibited viral growth.

5. Because viruses and their enzymes are capable of discriminating between enantiomeric forms of chiral molecules, I and others skilled in the field believed that

only one of the two possible enantiomeric nucleoside analogues would possess significant antiviral activity. Furthermore, we believed that because of the assumed molecular mimicry mechanism of action the enantiomer more closely resembling the natural stereochemical configuration of the native nucleosides, i.e., the "natural" enantiomer, would be the active enantiomer. We believed that the so-called "nonnatural" nucleoside analogue, on the other hand, would have little or no activity. It would not mimic the natural nucleoside properly for the virus to try and incorporate it.

6. These mechanism of action beliefs and expectations were borne out by experimental results reported in the literature. See, e.g., Exhibit A, entries 1-7 (corresponding to Table I in applicants' July 23, 1993 Response to the February 23, 1993 Office Action). Exhibit A sets forth the antiviral activity of seven different nucleoside analogues in enantiomerically enriched form and provides a side-by-side comparison between the activity of "natural"-"nonnatural" enantiomeric pairs. The data from entries 1-7 demonstrate exactly what we all believed: that as a general rule the "nonnatural" enantiomers do not possess significant antiviral activity.

7. However, contrary to my expectation and what I believe would have been the expectation of those of skill in

the art at the time, the (-)-enantiomer of this invention, i.e., the one possessing the "nonnatural" nucleoside configuration, has potent antiviral activity. See Tables 1 and 2 at page 28 of the application and Exhibit A, entry 8.

8. The (+)- and (-)-enantiomers were tested for cytotoxicity and the (-)-enantiomer of this invention was found to be significantly less toxic than its (+)-counterpart. See, e.g., Tables 1-3 at pages 28-29 of the '964 application. This difference in cytotoxicity was entirely unexpected for nucleoside analogues of essentially equal antiviral activity. This unexpected discovery challenged many of the dogmas that I and those skilled in the field of antiviral nucleosides had held prior to the invention disclosed in the '964 application. Before that invention, we had believed that antiviral activity and cytotoxicity went hand in hand. The low cytotoxicity of the (-)-enantiomer as compared to the (+)-enantiomer, together with its unexpectedly high level of anti-viral activity make the (-)-enantiomer particularly useful as a therapeutic agent. I believe that no one could have predicted that the (-)-enantiomer would have these advantageous properties.

9. Claim 3 of the '964 application claims the (-)-enantiomer in 95% purity. I believe and have no reason to doubt that mixtures containing 5% or less of the (+)-enantiomer would demonstrate surprising antiviral activity

and superior therapeutic index in comparison to the racemate or the (+)-enantiomer.

10. United States patents 5,047,407, 5,204,466 and the published PCT application WO 91/11186 refer to a racemic form of the (-)-enantiomer claimed in the '964 application. Nowhere in any of these documents, however, do I find a suggestion that would have challenged my expectations, or what I believe would have been the expectations of those skilled in the field, regarding the low antiviral activity of the (-)-enantiomer -- i.e., there is no suggestion in any of these documents that the "nonnatural" (-)-enantiomer would be as active as its "natural" (+) counterpart. More importantly, there is certainly no suggestion in any of these documents that the (-)-enantiomer would have a surprisingly improved therapeutic index.

11. As noted by the Examiner, United States patent 5,204,466 ("the '466 patent), column 4, lines 19-22 refers to "BCH-189 or BCH-189 analogs that are enantiomerically-enriched at the 4' position". However, throughout the '466 patent, in all figures, schemes and formulas, BCH-189 is presented in the "natural" configuration or in the (+)-enantiomeric form. This reflects the expectation, prior to the discovery of this application, that the active ingredient of racemic

nucleoside analogues is the enantiomer with the "natural" configuration. Therefore, the statement quoted by the Examiner, when considered in the context of the full description of the '466 patent and the level of skill in the art at the time the '466 patent was filed, not only fails to suggest that the (-)-enantiomer of BCH-189 would be as active as, or possess a higher therapeutic index than, its (+)-enantiomer.

12. I declare further that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, Title 18, United States Code, and that willful false statements may jeopardize the validity of this application and any patent issuing thereon.

Richard Storer

Richard Storer

Signed at: Greenford

Date: March 11th, 1994